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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/008,140	10/18/2001	Lieven Stuyver	08841.105021	2922

7590 04/25/2003

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EXAMINER
JOHANNSEN, DIANA B

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 04/25/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/008,140	STUYVER, LIEVEN	
	Examiner	Art Unit	
	Diana B. Johannsen	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 August 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-32* is/are rejected.

7)☒ Claim(s) *23-32* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *18 October 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *0302* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. The Preliminary Amendment filed March 11, 2002, and the paper and computer readable forms of the Sequence Listing filed August 30, 2002, have been entered.

Priority

2. The instant application claims benefit under 35 U.S.C. 119(e) of provisional applications 60/241,488, 60/256,067, and 60/282,156, and applicant has properly included the priority claim both in the Oath/Declaration and in the first line of the specification. However, it is noted that the claims under consideration are drawn to methods requiring a step of "contacting nucleic acids from a virus infected host with an amplification reaction mixture that contains at least two primers and/or probes that provide detectable signals during a polymerase chain reaction, wherein the first primer and/or probe provides a detectable signal on the occurrence of the transcription of viral nucleic acids; and the second primer and/or probe provides a second detectable signal on the occurrence of the transcription of host nucleic acids" to achieve the objective of identifying a compound which inhibits viral replication (claims 1-22), or a step of "contacting nucleic acids from a host with an amplification reaction mixture that contains at least two primers and/or probes that provide detectable signals during a polymerase chain reaction, wherein the first primer and/or probe provides a detectable signal on the occurrence on [sic] the transcription of host mitochondrial nucleic acids; and the second primer and/or probe provides a second detectable signal on the occurrence on [sic] the transcription of host nuclear nucleic acids" to achieve the objective of assessing the toxicity of a compound (claims 23-32). None of the listed provisional applications

discloses a method in which nucleic acids are contacted with an amplification mixture containing primers/probes that "provide a detectable signal" for both viral and host nucleic acid transcription to accomplish "identifying a compound which inhibits viral replication" as required by claims 1-22, or a method in which nucleic acids are contacted with an amplification mixture containing primers/probes that "provide a detectable signal" for both mitochondrial and nuclear nucleic acid transcription to accomplish "assessing the toxicity of a compound" as required by claims 23-32. Accordingly, the instant claims are not entitled to the filing date of any of the listed provisional applications. Rather, the effective filing date of the instant claims is the filing date of the instant application, i.e., **October 18, 2001** (see *Hunt Co. v Mallinckrodt Chemical Works*, 177 F.2d 583,587, 83 USPQ 277, 281; MPEP 201.11).

Information Disclosure Statement

3. Regarding the Information Disclosure Statement filed March 22, 2002, it is noted that the examiner has completed the citation for reference "CB" by providing the publication date of the reference (see page 6 of the initialed and signed copy of the Form 1449 enclosed herewith).

Specification

4. The use of the trademarks AMPLIFLUOR™, TAQMAN®, RNEASY®, SYBR®, PRIMER EXPRESS®, QIAAMP®, and AMPLICOR HIV-1 MONITOR™ has been noted in this application. The trademarks should be capitalized wherever they appear and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks.

Claim Objections

5. Claims 23-32 are objected to because of the following informalities. In independent claim 23, lines 5 and 7, the claim recites "occurrence on the transcription" rather than, e.g., "occurrence of the transcription" (as is recited in independent claim 1). Appropriate correction is required. This objection could be overcome by amending the claim to recite "of" rather than "on" in the phrase noted above.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1, 6, 10-11, 23, 26, and 30-31 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods employing a primer/probe that provides a detectable signal when transcription of a host β-actin gene and/or host GAPDH gene occurs, does not reasonably provide enablement for methods in which "the viral nucleic acid" is "from" β-actin or GAPDH, or for methods in which "the host mitochondrial nucleic acid" is a non-coding sequence "from" β-actin or GAPDH. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (A) the breadth of the claims; (B) the nature of the invention; (C) the state of the prior art; (D) the level of one of ordinary skill; (E) the level of predictability in the art; (F) the amount of direction provided by the inventor; (G) the existence of working examples; and (H) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (*MPEP* 2164.01(a)).

Claims 1, 6, 10 and 11 are drawn to a method for "identifying a compound which inhibits viral replication that includes contacting nucleic acids from a virus infected host with an amplification reaction mixture that contains at least two primers and/or probes that provide detectable signals during a polymerase chain reaction, wherein the first primer and/or probe provides a detectable signal on the occurrence of the transcription of viral nucleic acids; and the second primer and/or probe provides a second detectable signal on the occurrence of the transcription of host nucleic acids;" claim 6 further requires that "the viral nucleic acid is a non-coding sequence," while claim 10 states that 'the non-coding sequence is from β-actin," and claim 11 states that "the non-coding sequence is from GAPDH." Claims 23, 26, 30 and 31 are drawn to a method for "assessing the toxicity of a compound that includes contacting nucleic acids from a host with an amplification reaction mixture that contains at least two primers and/or probes that provide detectable signals during a polymerase chain reaction, wherein the first

primer and/or probe provides a detectable signal on the occurrence on [sic] the transcription of host mitochondrial nucleic acids; and the second primer and/or probe provides a second detectable signal on the occurrence on [sic] the transcription of host nuclear nucleic acids;" claim 26 further requires that "the host mitochondrial nucleic acid is a non-coding sequence," while claim 30 states that 'the non-coding sequence is from β-actin," and claim 31 states that "the non-coding sequence is from GAPDH."

It is noted that claims 10-11 as written are drawn to methods in which "the viral nucleic acid is a non-coding sequence" (see claim 6), and further in which "the non-coding sequence is from β-actin" (claim 10) or "the non-coding sequence is from GAPDH" (claim 11). Claims 30-31 as written are drawn to methods in which "the host mitochondrial nucleic acid is a non-coding sequence" (see claim 26) and further in which 'the non-coding sequence is from β-actin" (claim 30) or "the non-coding sequence is from GAPDH" (claim 31). However, the teachings of applicant's specification and of the prior art (as discussed in more detail below) make clear that β-actin and GAPDH are in fact host cell nuclear genes, rather than viral genes or host mitochondrial genes. As the invention disclosed in the specification is described as a method in which β-actin and/or GAPDH transcripts serve as indicators of transcription of host nuclear genes (rather than viral genes and/or host mitochondrial genes, as recited in the claims), claims 10-11 have been treated as encompassing both methods in which β-actin/GAPDH constitute further limitations of "host nucleic acids"/ "nuclear nucleic acid," and methods in which "the viral nucleic acid is a non-coding sequence" from β-actin (claim 10)/from GAPDH (claim 11). This rejection applies to claims 1 and 6 to the

extent that they are drawn to the invention of claims 10-11. Similarly, claims 30-31 have been treated as encompassing both methods in which β-actin/GAPDH constitute further limitations of "host nuclear nucleic acid," and methods in which "the viral nucleic acid is a non-coding sequence" from β-actin (claim 30)/from GAPDH (claim 31). This rejection applies to claims 23 and 26 to the extent that they are drawn to the invention of claims 30-31. **This rejection could be overcome by amending claims 10-11 and 30-31 such that the claims are further limiting of host nucleic acids/host nuclear nucleic acids.**

It is unpredictable as to whether one of skill could use applicant's invention in a manner reasonably commensurate with the instant claims. The specification teaches and exemplifies methods in which nuclear host cell genes β-actin and GAPDH are employed (see entire specification, particularly Figures 4-5; Examples 5, 11-12, 15; see also pages 15, 23, 33); in these methods, the transcription of host cell nuclear genes is compared either with transcription of a viral gene (in methods of identifying antiviral agents, such as the methods of instant claim 1) or with transcription of a host mitochondrial gene (in methods assaying for toxicity, such as the methods of instant claim 23). The specification does not describe or provide examples of the use of viral β-actin or GAPDH genes, or mitochondrial β-actin or GAPDH genes. Further, the specification clearly indicates at page 33 that the β-actin gene is a host nuclear gene (see in particular, lines 11-12; see also page 63, lines 4-6). Similarly, the teachings of the prior art, as exemplified by Ng et al (Molecular and Cellular Biology 5(10):2720-2732 [10/1985]; see entire reference, particularly page 2722), disclose a nuclear β-actin

functional gene. The specification does not state that the GAPDH gene disclosed therein is a nuclear gene. However, the teachings of the prior art, as exemplified by Thomas et al (Clinical Science 97:207-213 [8/1999]; see entire reference, particularly Figure 1) and Ercolani et al (The Journal of Biological Chemistry 263(30):15335-15341, see entire reference, particularly, e.g., page 15339 and Figure 8), disclose that the GAPDH gene is a nuclear gene. Accordingly, both the teachings of the specification and of the prior art indicate that the genes for β-actin and GAPDH are nuclear genes. The teachings of the specification make clear that the methods of the invention require the detection of different specific target nucleic acids in virus as compared to host cell, or in mitochondria as compared to nucleus, such that levels of transcription in virus as compared to host, or in mitochondria as compared to nucleus, may be accurately compared. Further, it would be readily apparent to one of skill in the art, given the teachings of the specification and of the art, that detection of β-actin or GAPDH transcripts during the practice of the method disclosed in applicant's specification would not reflect viral gene or mitochondrial gene transcription, but rather nuclear gene transcription, and despite the high level of skill of one skilled in the relevant art, no quantity of experimentation would be sufficient to alter this fact. Accordingly, to the extent that the instant claims are drawn to methods in which "the viral nucleic acid" is "from β-actin" or "from GAPDH," and to methods in which "the host mitochondrial nucleic acid" is "from β-actin" or "from GAPDH," the teachings of the specification and of the art are insufficient to enable one of skill in the art to use the claimed invention. While one of skill could practice methods employing a primer/probe that provides a

detectable signal when transcription of a host nuclear β-actin gene and/or host nuclear GAPDH gene occurs, it would require undue experimentation to use applicant's invention in a manner reasonably commensurate with the claims.

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 1-32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-22 are indefinite because it is unclear as to how the practice of the method steps required by the claims allows one to achieve the objective of "identifying a compound which inhibits viral replication," as recited in the preamble of claim 1. The claims merely require a step of "contacting nucleic acids from a virus infected host with an amplification reaction mixture that contains at least two primers and/or probes that provide detectable signals during a polymerase chain reaction, wherein the first primer and/or probe provides a detectable signal on the occurrence of the transcription of viral nucleic acids; and the second primer and/or probe provides a second detectable signal on the occurrence of the transcription of host nucleic acids." The claim does not include any method step in which a "compound" is employed, nor does the claim language make clear how the step of "contacting" nucleic acids with the "primers and/or probes" allows one to identify a "compound which inhibits viral replication." Accordingly, the claims are vague and indefinite, and it is unclear as to whether the claims are intended

to be drawn to a method for "identifying a compound which inhibits viral replication," or to a method of contacting nucleic acids with primers and/or probes.

Claims 1-22 are indefinite over the recitation of the phrases "at least two primers and/or probes," "the first primer and/or probe," and "the second primer and/or probe" in claim 1. First, there is insufficient antecedent basis for the recitations "the first primer and/or probe" and "the second primer and/or probe," as claim 1 does not previously refer to a "first" or "second" "primer and/or probe." Additionally, it is unclear from the language of the claim as to whether applicant's intent is for the claims to require the use of at least two molecules, wherein each molecule may have the properties of a primer and/or a probe (as suggested by the recitations "the first primer and/or probe provides..." and "the second primer and/or probe provides..."), or whether the claims are intended to also encompass "at least two" pairs of molecules (e.g., a first primer and first probe, and a second primer and second probe), as well as combinations of "at least" two molecules in which a "first" molecule is a primer and "second" molecule is a probe, etc. Accordingly, clarification is required so as to apprise one of skill in the art as to what types of molecules and combinations thereof are actually encompassed by the claims.

Claims 1-22 are indefinite over the recitation of the language "the occurrence of the transcription of viral nucleic acids" in claim 1. As the claim does not previously refer to transcription or to any "occurrence of" transcription, there is insufficient antecedent basis for the limitations "the transcription" and "the occurrence of the transcription."

Claims 2-5 are indefinite over the recitation of the limitation "the host nucleic acid" in claims 2-3. There is insufficient antecedent basis for this recitation in the claims, as claim 1 refers to "host nucleic acids," but not to a "host nucleic acid."

Claims 6-11 are indefinite over the recitation of the limitation "the viral nucleic acid" in claim 6. There is insufficient antecedent basis for this recitation in the claims, as claim 1 refers to "viral nucleic acids," but not to a "viral nucleic acid."

Claims 10-11 are indefinite over the recitation of the limitations "wherein the non-coding sequence is from β-actin" and "wherein the non-coding sequence is from GAPDH," respectively. These recitations are unclear because β-actin and GAPDH are proteins, whereas the claims are further limiting of a nucleic acid. It is unclear as to how a requirement that a nucleic acid be "from" a particular protein might further limit the structures intended to be encompassed by the claims. Clarification is required.

Claims 12-22 are indefinite over the recitation of the limitation "the viral nucleic acid" in claim 12. There is insufficient antecedent basis for this recitation in the claims, as claim 1 refers to "viral nucleic acids," but not to a "viral nucleic acid."

Claims 18-19 are indefinite over the recitation of the limitations "wherein the coding sequence is from herpes" and "wherein the coding sequence is from influenza," respectively. These recitations are unclear because herpes and influenza are diseases/conditions, rather than infectious agents from which nucleic acids might be obtained. This rejection could be overcome by amending the claims to recite "wherein the coding sequence is from a herpes virus" and "wherein the coding sequence is from an influenza virus," respectively.

Claims 23-32 are indefinite because it is unclear as to how the practice of the method steps required by the claims allows one to achieve the objective of "assessing the toxicity of a compound," as recited in the preamble of claim 23. The claims merely require a step of "contacting nucleic acids from a host with an amplification reaction mixture that contains at least two primers and/or probes that provide detectable signals during a polymerase chain reaction, wherein the first primer and/or probe provides a detectable signal on the occurrence on [sic] the transcription of host mitochondrial nucleic acids; and the second primer and/or probe provides a second detectable signal on the occurrence on [sic] the transcription of host nuclear nucleic acids." The claim does not include any method step in which a "compound" is employed, nor does the claim language make clear how the step of "contacting" nucleic acids with the "primers and/or probes" would allow one to accomplish "assessing the toxicity of a compound." Accordingly, the claims are vague and indefinite, and it is unclear as to whether the claims are intended to be drawn to a method for "assessing the toxicity of a compound" or to a method of contacting nucleic acids with primers and/or probes.

Claims 23-32 are indefinite over the recitation of the phrases "at least two primers and/or probes," "the first primer and/or probe," and "the second primer and/or probe" in claim 23. First, there is insufficient antecedent basis for the recitations "the first primer and/or probe" and "the second primer and/or probe," as claim 23 does not previously refer to a "first" or "second" "primer and/or probe." Additionally, it is unclear from the language of the claim as to whether applicant's intent is for the claims to require the use of at least two molecules, wherein each molecule may have the

properties of a primer and/or a probe (as suggested by the recitations "the first primer and/or probe provides..." and "the second primer and/or probe provides..."), or whether the claims are intended to also encompass "at least two" pairs of molecules (e.g., a first primer and first probe, and a second primer and second probe), as well as combinations of "at least" two molecules in which a "first" molecule is a primer and "second" molecule is a probe, etc. Accordingly, clarification is required so as to apprise one of skill in the art as to what types of molecules and combinations thereof are actually encompassed by the claims.

Claims 23-32 are indefinite over the recitation of the language "the occurrence on [sic] the transcription of viral nucleic acids" in claim 23. As the claim does not previously refer to transcription or to any "occurrence of" transcription, there is insufficient antecedent basis for the limitations "the transcription" and "the occurrence on the transcription."

Claims 24-32 are indefinite over the recitation of the limitation "the host mitochondrial nucleic acid" in claims 24-26 and 32. There is insufficient antecedent basis for this recitation in the claims, as claim 23 refers to "host mitochondrial nucleic acids," but not to a "host mitochondrial nucleic acid."

Claims 30-31 are indefinite over the recitation of the limitations "wherein the non-coding sequence is from β-actin" and "wherein the non-coding sequence is from GAPDH," respectively. These recitations are unclear because β-actin and GAPDH are proteins, whereas the claims are further limiting of a nucleic acid. It is unclear as to how

a requirement that a nucleic acid be "from" a particular protein might further limit the structures intended to be encompassed by the claims. Clarification is required.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

11. Claims 1-2 and 12 are rejected under 35 U.S.C. 102(e) as being clearly anticipated by Hall et al (U.S. Patent No. 6,218,105 B1 [04/17/2001; filed 01/07/2000; effective filing date 01/08/1999]).

Regarding the effective filing date of U.S. Patent No. 6,218,105, it is noted that the '105 patent claims the benefit of U.S. provisional application 60/115,220, filed January 8, 1999, and that the subject matter used to make the instant rejection is supported by the provisional application.

Hall et al disclose a method for "large scale screening of antiviral agents" (see entire reference, particularly, e.g., column 2, line 46-column 4, line 7). In embodiments of Hall et al's method, virions (both pre-incubated with a test agent and an untreated control) are used to infect host cells, and viral and host cell mRNA's are then PCR amplified in a single reaction mixture to determine the effects of the test agent on

transcription (see col 2, line 46-column 4, line 7 [particularly col 2, lines 64-66, col 3, lines 38-39]; col 4, line 62-col 5, lines 1-8; col 5, lines 32-36; col 6, line 19-col 8, line 19 [particularly col 7, line 56-67, describing real-time PCR detection of viral and cellular control transcripts in a single tube]). Hall et al disclose the use of both primers and probes that produce different detectable signals as indicators of viral nucleic acid transcription as compared to host nucleic acid transcription (see, e.g., col 7, line 56-col 8, line 1-19). It is also noted that Hall et al exemplify the use of their methods in determining whether patient sera contains neutralizing antibodies capable of preventing HPV-11 replication (see, e.g., col 8, lines 51-64). Regarding claim 2, it is an inherent property of the GAPDH host cell transcripts taught by Hall et al (see, e.g., col 7, lines 1-67; column 8, lines 1-19) that they are transcripts of nuclear nucleic acids. Regarding claim 12, Hall et al disclose detection of viral mRNA (as discussed above), and exemplify the use in their methods of the E2 mRNA of HPV-11 as their indicator of viral transcription (see, e.g., Figure 2, col 3, lines 40-43; column 6, line 21-column 8, line 19 [particularly column 7, lines 56-67, describing real-time PCR detection of E2 and cellular control transcripts in a single tube]). It is an inherent property of any mRNA (including the E2 mRNA exemplified by Hall et al) that it is a "coding sequence", and further it is an inherent property of the primers/probes of Hall et al that detect viral mRNA that they provide a detectable signal "on the occurrence" of the transcription of a viral nucleic acid that "is a coding sequence." Accordingly, Hall et al anticipate claims 1-2 and 12.

12. Claims 1-2 and 12 are rejected under 35 U.S.C. 102(a) as being clearly anticipated by Hall et al (U.S. Patent No. 6,218,105 B1 [04/17/2001; filed 01/07/2000]).

Hall et al disclose a method for "large scale screening of antiviral agents" (see entire reference, particularly, e.g., column 2, line 46-column 4, line 7). In embodiments of Hall et al's method, virions (both pre-incubated with a test agent and an untreated control) are used to infect host cells, and viral and host cell mRNA's are then PCR amplified in a single reaction mixture to determine the effects of the test agent on transcription (see col 2, line 46-column 4, line 7 [particularly col 2, lines 64-66, col 3, lines 38-39]; col 4, line 62-col 5, lines 1-8; col 5, lines 32-36; col 6, line 19-col 8, line 19 [particularly col 7, line 56-67, describing real-time PCR detection of viral and cellular control transcripts in a single tube]). Hall et al disclose the use of both primers and probes that produce different detectable signals as indicators of viral nucleic acid transcription as compared to host nucleic acid transcription (see, e.g., col 7, line 56-col 8, line 1-19). It is also noted that Hall et al exemplify the use of their methods in determining whether patient sera contains neutralizing antibodies capable of preventing HPV-11 replication (see, e.g., col 8, lines 51-64). Regarding claim 2, it is an inherent property of the GAPDH host cell transcripts taught by Hall et al (see, e.g., col 7, lines 1-67; column 8, lines 1-19) that they are transcripts of nuclear nucleic acids. Regarding claim 12, Hall et al disclose detection of viral mRNA (as discussed above), and exemplify the use in their methods of the E2 mRNA of HPV-11 as their indicator of viral transcription (see, e.g., Figure 2, col 3, lines 40-43; column 6, line 21-column 8, line 19 [particularly column 7, lines 56-67, describing real-time PCR detection of E2 and cellular control transcripts in a single tube]). It is an inherent property of any mRNA (including the E2 mRNA exemplified by Hall et al) that it is a "coding sequence", and further it is an

inherent property of the primers/probes of Hall et al that detect viral mRNA that they provide a detectable signal "on the occurrence" of the transcription of a viral nucleic acid that "is a coding sequence." Accordingly, Hall et al anticipate claims 1-2 and 12.

13. Claims 6-9 are rejected under 35 U.S.C. 102(e) as being clearly anticipated by Hall et al (U.S. Patent No. 6,218,105 B1 [04/17/2001; filed 01/07/2000; effective filing date 01/08/1999]), in light of the teachings of Crooke et al (U.S. Patent No. 5,756,282 A [5/1998]).

Regarding the effective filing date of U.S. Patent No. 6,218,105, it is noted that the '105 patent claims the benefit of U.S. provisional application 60/115,220, filed January 8, 1999, and that the subject matter used to make the instant rejection is supported by the provisional application.

Hall et al disclose a method for "large scale screening of antiviral agents" (see entire reference, particularly, e.g., column 2, line 46-column 4, line 7). In embodiments of Hall et al's method, virions (both pre-incubated with a test agent and an untreated control) are used to infect host cells, and viral and host cell mRNA's are then PCR amplified in a single reaction mixture to determine the effects of the test agent on transcription (see col 2, line 46-column 4, line 7 [particularly col 2, lines 64-66, col 3, lines 38-39]; col 4, line 62-col 5, lines 1-8; col 5, lines 32-36; col 6, line 19-col 8, line 19 [particularly col 7, lines 56-67, describing real-time PCR detection of viral and cellular control transcripts in a single tube]). Hall et al disclose the use of both primers and probes that produce different detectable signals as indicators of viral nucleic acid transcription as compared to host nucleic acid transcription (see, e.g., col 7, line 56-col

8, line 1-19). It is also noted that Hall et al exemplify the use of their methods in determining whether patient sera contains neutralizing antibodies capable of preventing HPV-11 replication (see, e.g., col 8, lines 51-64). Hall et al disclose the use in their methods of the E2 mRNA of HPV-11 as their indicator of viral transcription (see, e.g., Figure 2, col 3, lines 40-43; column 6, line 21-column 8, line 19 [particularly column 7, lines 56-67, describing real-time PCR detection of E2 and cellular control transcripts in a single tube]). Crooke et al disclose that it an inherent property of the E2 mRNAs of papilloma viruses that they includes non-coding sequences, including both 5' and 3' non-coding sequences (see entire reference, particularly Figure 2), and further than the nucleic acids from which E2 is transcribed include an E5 intron (see, in particular, Figure 2). Thus, the teachings of Crooke et al establish that it is an inherent property of the primers/probes to E2 taught by Hall et al that they provide a detectable signal "on the occurrence of the transcription" of a viral nucleic acid that is a "non-coding sequence," and that the non-coding sequences transcribed include 5' and 3' non-coding sequences and intron sequences. Accordingly, Hall et al anticipate claims 6-9.

14. Claims 6-9 are rejected under 35 U.S.C. 102(a) as being clearly anticipated by Hall et al (U.S. Patent No. 6,218,105 B1 [04/17/2001; filed 01/07/2000]), in light of the teachings of Crooke et al (U.S. Patent No. 5,756,282 A [5/1998]).

Hall et al disclose a method for "large scale screening of antiviral agents" (see entire reference, particularly, e.g., column 2, line 46-column 4, line 7). In embodiments of Hall et al's method, virions (both pre-incubated with a test agent and an untreated control) are used to infect host cells, and viral and host cell mRNA's are then PCR

amplified in a single reaction mixture to determine the effects of the test agent on transcription (see col 2, line 46-column 4, line 7 [particularly col 2, lines 64-66, col 3, lines 38-39]; col 4, line 62-col 5, lines 1-8; col 5, lines 32-36; col 6, line 19-col 8, line 19 [particularly col 7, lines 56-67, describing real-time PCR detection of viral and cellular control transcripts in a single tube]). Hall et al disclose the use of both primers and probes that produce different detectable signals as indicators of viral nucleic acid transcription as compared to host nucleic acid transcription (see, e.g., col 7, line 56-col 8, line 1-19). It is also noted that Hall et al exemplify the use of their methods in determining whether patient sera contains neutralizing antibodies capable of preventing HPV-11 replication (see, e.g., col 8, lines 51-64). Hall et al disclose the use in their methods of the E2 mRNA of HPV-11 as their indicator of viral transcription (see, e.g., Figure 2, col 3, lines 40-43; column 6, line 21-column 8, line 19 [particularly column 7, lines 56-67, describing real-time PCR detection of E2 and cellular control transcripts in a single tube]). Crooke et al disclose that it an inherent property of the E2 mRNAs of papilloma viruses that they comprise non-coding sequences, including both 5' and 3' non-coding sequences (see entire reference, particularly Figure 2), and further than the nucleic acids from which E2 is transcribed include an E5 intron (see, in particular, Figure 2). Thus, the teachings of Crooke et al establish that it is an inherent property of the primers/probes to E2 taught by Hall et al that they provide a detectable signal "on the occurrence of the transcription" of a viral nucleic acid that is a "non-coding sequence," and that the non-coding sequences transcribed include 5' and 3' non-coding sequences and intron sequences. Accordingly, Hall et al anticipate claims 6-9.

15. Claim 11 is rejected under 35 U.S.C. 102(e) as being clearly anticipated by Hall et al (U.S. Patent No. 6,218,105 B1 [04/17/2001; filed 01/07/2000; effective filing date 01/08/1999]), in light of the teachings of Ercolani et al (The Journal of Biological Chemistry 263(30):15335-15341 [1988]).

Regarding the effective filing date of U.S. Patent No. 6,218,105, it is noted that the '105 patent claims the benefit of U.S. provisional application 60/115,220, filed January 8, 1999, and that the subject matter used to make the instant rejection is supported by the provisional application.

This rejection applies to the claim to the extent that it is intended to be drawn to methods in which "the host nucleic acid" (rather than "the viral nucleic acid") is a "non-coding sequence," and in which "the non-coding sequence is from GAPDH." Please also see paragraph 7, above.

Hall et al disclose a method for "large scale screening of antiviral agents" (see entire reference, particularly, e.g., column 2, line 46-column 4, line 7). In embodiments of Hall et al's method, virions (both pre-incubated with a test agent and an untreated control) are used to infect host cells, and viral and host cell mRNA's are then PCR amplified in a single reaction mixture to determine the effects of the test agent on transcription (see col 2, line 46-column 4, line 7 [particularly col 2, lines 64-66, col 3, lines 38-39]; col 4, line 62-col 5, lines 1-8; col 5, lines 32-36; col 6, line 19-col 8, line 19 [particularly col 7, line 56-67, describing real-time PCR detection of viral and cellular control transcripts in a single tube]). Hall et al disclose the use of both primers and probes that produce different detectable signals as indicators of viral nucleic acid

transcription as compared to host nucleic acid transcription (see, e.g., col 7, line 56-col 8, line 1-19). It is also noted that Hall et al exemplify the use of their methods in determining whether patient sera contains neutralizing antibodies capable of preventing HPV-11 replication (see, e.g., col 8, lines 51-64). Hall et al disclose the use in their methods of human cells (see, e.g., col 5, lines 23-27; see also col 2, lines 66-67; col 4, line 67-col 5, line 1), and further disclose the use in their methods of GAPDH transcripts as the host cell mRNA control (see, e.g., col 7, lines 1-67; column 8, lines 1-19). Ercolani et al disclose that it an inherent property of human GAPDH mRNA that it includes non-coding sequences (see entire reference, particular page 15335, right column, and Figure 3). Thus, the teachings of Ercolani et al establish that it is an inherent property of the primers/probes to GAPDH taught by Hall et al that they provide a detectable signal "on the occurrence of the transcription" of a host nucleic acid that is a "non-coding sequence." Accordingly, Hall et al anticipate claim 11.

16. Claim 11 is rejected under 35 U.S.C. 102(a) as being clearly anticipated by Hall et al (U.S. Patent No. 6,218,105 B1 [04/17/2001; filed 01/07/2000]), in light of the teachings of Ercolani et al (The Journal of Biological Chemistry 263(30):15335-15341 [1988]).

This rejection applies to the claim to the extent that it is intended to be drawn to methods in which "the host nucleic acid" (rather than "the viral nucleic acid") is a "non-coding sequence," and in which "the non-coding sequence is from GAPDH." Please also see paragraph 7, above.

Hall et al disclose a method for "large scale screening of antiviral agents" (see entire reference, particularly, e.g., column 2, line 46-column 4, line 7). In embodiments of Hall et al's method, virions (both pre-incubated with a test agent and an untreated control) are used to infect host cells, and viral and host cell mRNA's are then PCR amplified in a single reaction mixture to determine the effects of the test agent on transcription (see col 2, line 46-column 4, line 7 [particularly col 2, lines 64-66, col 3, lines 38-39]; col 4, line 62-col 5, lines 1-8; col 5, lines 32-36; col 6, line 19-col 8, line 19 [particularly col 7, line 56-67, describing real-time PCR detection of viral and cellular control transcripts in a single tube]). Hall et al disclose the use of both primers and probes that produce different detectable signals as indicators of viral nucleic acid transcription as compared to host nucleic acid transcription (see, e.g., col 7, line 56-col 8, line 1-19). It is also noted that Hall et al exemplify the use of their methods in determining whether patient sera contains neutralizing antibodies capable of preventing HPV-11 replication (see, e.g., col 8, lines 51-64). Hall et al disclose the use in their methods of human cells (see, e.g., col 5, lines 23-27; see also col 2, lines 66-67; col 4, line 67-col 5, line 1), and further disclose the use in their methods of GAPDH transcripts as the host cell mRNA control (see, e.g., col 7, lines 1-67; column 8, lines 1-19). Ercolani et al disclose that it an inherent property of human GAPDH mRNA that it includes non-coding sequences (see entire reference, particular page 15335, right column, and Figure 3). Thus, the teachings of Ercolani et al establish that it is an inherent property of the primers/probes to GAPDH taught by Hall et al that they provide

a detectable signal "on the occurrence of the transcription" of a host nucleic acid that is a "non-coding sequence." Accordingly, Hall et al anticipate claim 11.

Claim Rejections - 35 USC § 103

17. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

18. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

19. Claims 3-5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hall et al (U.S. Patent No. 6,218,105 B1 [04/17/2001; filed 01/07/2000; effective filing date 01/08/1999]) in view of Pan-Zhou et al (Antimicrobial Agents and Chemotherapy 44(3):496-503 [3/2000]).

Regarding the effective filing date of U.S. Patent No. 6,218,105, it is noted that the '105 patent claims the benefit of U.S. provisional application 60/115,220, filed

January 8, 1999, and that the subject matter used to make the instant rejection is supported by the provisional application.

Hall et al disclose a method for "large scale screening of antiviral agents" (see entire reference, particularly, e.g., column 2, line 46-column 4, line 7). In embodiments of Hall et al's method, virions (both pre-incubated with a test agent and an untreated control) are used to infect host cells, and viral and host cell mRNA's are then PCR amplified in a single reaction mixture to determine the effects of the test agent on transcription (see col 2, line 46-column 4, line 7 [particularly col 2, lines 64-66, col 3, lines 38-39]; col 4, line 62-col 5, lines 1-8; col 5, lines 32-36; col 6, line 19-col 8, line 19 [particularly col 7, line 56-67, describing real-time PCR detection of viral and cellular control transcripts in a single tube]). Hall et al disclose the use of both primers and probes that produce different detectable signals as indicators of viral nucleic acid transcription as compared to host nucleic acid transcription (see, e.g., col 7, line 56-col 8, line 1-19). It is also noted that Hall et al exemplify the use of their methods in determining whether patient sera contains neutralizing antibodies capable of preventing HPV-11 replication (see, e.g., col 8, lines 51-64). Hall et al disclose the use in their methods of human cells (see, e.g., col 5, lines 23-27; see also col 2, lines 66-67; col 4, line 67-col 5, line 1), and further disclose the use in their methods of GAPDH transcripts as the host cell mRNA control (see, e.g., col 7, lines 1-67; column 8, lines 1-19). However, Hall et al do not disclose the detection in their methods of host mitochondrial transcripts.

Pan-Zhou et al disclose that different antiviral agents may cause different types of toxic effects on human mitochondria, including inhibition of mitochondrial DNA replication and protein synthesis (see entire reference, particularly page 501). In view of the teachings of Pan-Zhou et al, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Hall et al so as to have detected mitochondrial mRNA in addition to or in lieu of another host mRNA (such as the GAPDH exemplified by Hall et al). This modification would further require the design and use in Hall et al's method of primers and/or probes that provide a detectable signal "on the occurrence of the transcription" of mitochondrial nucleic acid. An ordinary artisan would have been motivated to have made such a modification in order to have simultaneously detected the effects of potential antiviral agents on both viral transcription and mitochondrial mRNA levels, for the advantage of rapidly assessing the potential effectiveness and safety of a novel antiviral compound in treating an infected subject. Regarding claims 4-5, it is noted that transcription of mitochondrial DNA results in the production of mitochondrial RNA, and that it is a property of the primers/probes suggested by Hall et al in view of Pan-Zhou et al that they would provide a detectable signal "on the occurrence of the transcription" of either mitochondrial DNA or mitochondrial RNA.

20. Claim 10 is rejected under 35 U.S.C. 103(a) as being unpatentable over Hall et al (U.S. Patent No. 6,218,105 B1 [04/17/2001; filed 01/07/2000; effective filing date 01/08/1999]), in light of the teachings of Ng et al (Molecular and Cellular Biology 5(10):2720-2732 [10/1985]).

Regarding the effective filing date of U.S. Patent No. 6,218,105, it is noted that the '105 patent claims the benefit of U.S. provisional application 60/115,220, filed January 8, 1999, and that the subject matter used to make the instant rejection is supported by the provisional application.

This rejection applies to the claim to the extent that it is intended to be drawn to methods in which "the host nucleic acid" (rather than "the viral nucleic acid") is a "non-coding sequence," and in which "the non-coding sequence is from β-actin." Please also see paragraph 7, above.

Hall et al disclose a method for "large scale screening of antiviral agents" (see entire reference, particularly, e.g., column 2, line 46-column 4, line 7). In embodiments of Hall et al's method, virions (both pre-incubated with a test agent and an untreated control) are used to infect host cells, and viral and host cell mRNA's are then PCR amplified in a single reaction mixture to determine the effects of the test agent on transcription (see col 2, line 46-column 4, line 7 [particularly col 2, lines 64-66, col 3, lines 38-39]; col 4, line 62-col 5, lines 1-8; col 5, lines 32-36; col 6, line 19-col 8, line 19 [particularly col 7, line 56-67, describing real-time PCR detection of viral and cellular control transcripts in a single tube]). Hall et al disclose the use of both primers and probes that produce different detectable signals as indicators of viral nucleic acid transcription as compared to host nucleic acid transcription (see, e.g., col 7, line 56-col 8, line 1-19). It is also noted that Hall et al exemplify the use of their methods in determining whether patient sera contains neutralizing antibodies capable of preventing HPV-11 replication (see, e.g., col 8, lines 51-64). Hall et al disclose the use in their

methods of human cells (see, e.g., col 5, lines 23-27; see also col 2, lines 66-67; col 4, line 67-col 5, line 1), and further disclose the use in their methods of GAPDH transcripts as the host cell mRNA control (see, e.g., col 7, lines 1-67; column 8, lines 1-19).

Hall et al do not disclose the use of β-actin transcripts as a control in the "single-tube" embodiments of their invention. However, Hall et al exemplify the use of β-actin transcripts as a control in a virus titration in which viral transcripts are also detected (see Figure 3 and col 8, lines 32-47). Further, Hall et al merely state that their method requires a "host cell transcript" (see, e.g., col 3, lines 38-39), and do not provide any indication that their single-tube method of antiviral screening requires the use of the particular control (GAPDH) exemplified in the specification. Accordingly, in view of the teachings of Hall et al, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified the single-tube antiviral screening method of Hall et al so as to have detected as the host control transcript β-actin mRNA rather than GAPDH mRNA, and to have prepared the labeled β-actin primers/probes necessary for use in such a method, which primers/probes would provide a detectable signal "on the occurrence of the transcription" of β-actin nucleic acids. An ordinary artisan would have been motivated to have made such a modification in instances when β-actin probes/primers were more readily available to the practitioner, for the advantage of convenience, and/or in instances when the artisan wished to perform both the virus titration assay exemplified by Hall et al (in which β-actin is employed, as discussed above) and a single-tube method of antiviral screening,

so as to have been able to use the same or similar primers in both assays, for the advantages of efficiency and cost-effectiveness in performing both assays.

Ng et al disclose that it is a property of human β-actin mRNA that it includes non-coding sequences (see entire reference, particularly page 2725, including Figure 4). Thus, the teachings of Ng et al establish that it is a property of human β-actin mRNA that it is a product of the transcription of "a non-coding sequence." Accordingly, it would be a property of the probes/primers employed in the method suggested by Hall et al (discussed immediately above) that they provide a detectable signal "on the occurrence of the transcription" of a host nucleic acid that is a "non-coding sequence."

21. Claims 13-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hall et al (U.S. Patent No. 6,218,105 B1 [04/17/2001; filed 01/07/2000; effective filing date 01/08/1999]) in view of Barney et al (U.S. Patent No. 6,054,265 A [4/2000]).

Regarding the effective filing date of U.S. Patent No. 6,218,105, it is noted that the '105 patent claims the benefit of U.S. provisional application 60/115,220, filed January 8, 1999, and that the subject matter used to make the instant rejection is supported by the provisional application.

Hall et al disclose a method for "large scale screening of antiviral agents" (see entire reference, particularly, e.g., column 2, line 46-column 4, line 7). In embodiments of Hall et al's method, virions (both pre-incubated with a test agent and an untreated control) are used to infect host cells, and viral and host cell mRNA's are then PCR amplified in a single reaction mixture to determine the effects of the test agent on transcription (see col 2, line 46-column 4, line 7 [particularly col 2, lines 64-66, col 3,

lines 38-39]; col 4, line 62-col 5, lines 1-8; col 5, lines 32-36; col 6, line 19-col 8, line 19 [particularly col 7, lines 56-67, describing real-time PCR detection of viral and cellular control transcripts in a single tube]). Hall et al disclose the use of both primers and probes that produce different detectable signals as indicators of viral nucleic acid transcription as compared to host nucleic acid transcription (see, e.g., col 7, line 56-col 8, line 1-19). It is also noted that Hall et al exemplify the use of their methods in determining whether patient sera contains neutralizing antibodies capable of preventing HPV-11 replication (see, e.g., col 8, lines 51-64). Hall et al disclose detection of viral mRNA (as discussed above), and exemplify the use in their methods of the E2 mRNA of HPV-11 as their indicator of viral transcription (see, e.g., Figure 2, col 3, lines 40-43; column 6, line 21-column 8, line 19 [particularly column 7, lines 56-67, describing real-time PCR detection of E2 and cellular control transcripts in a single tube]). It is a property of any mRNA (including the E2 mRNA exemplified by Hall et al) that it is a "coding sequence", and further it is a property of the primers/probes of Hall et al that detect viral mRNA that they provide a detectable signal "on the occurrence" of the transcription of a viral nucleic acid that "is a coding sequence." However, while Hall et al teach that their method may be used to screen for antiviral agents that inhibit other HPV types "as well as other viruses" (see col 2, lines 50-52) and state that "the invention may be used for identification of antiviral agents for various viruses, both human and non-human" (col 4, lines 58-60), Hall et al do not disclose the use of their methods in screening for antiviral agents that inhibit any of the types of viruses recited in claims 13-22.

Like Hall et al, Barney et al teach methods of screening for antiviral activity (see entire reference, particularly col 894, line 52-col 901, line 10). Barney et al disclose antiviral peptides, and teach that their antiviral peptides may inhibit a variety of viruses (see col 896, lines 21-24, and Tables V-VII and IX-XIV), including HIV (see, e.g., Table V at col 41-44), HBV (see, e.g., Table V at col 33-34, 35-36), HCV (see, e.g., Table V at col 79-82), BVDV (see, e.g., Table V at col 77-78), West Nile Virus (see, e.g., Table V at col 85-86), the herpes viruses herpes simplex (see, e.g., Table V at col 29-30, col 35-38), EBV (see, e.g., Table V at col 29-30, 35-38) and CMV (see, e.g., Table V at col 35-36), influenza viruses (see, e.g., Table V at col 51-col 60), and RSV (see, e.g., Table V at col 69-70). Accordingly, Barney et al teach that a need exists for antiviral agents capable of inhibiting each of the above listed virus types, and suggest screening to identify such agents. In view of the teachings of Barney et al, it would have been *prima facie* obvious to one of ordinary skill in the art to have modified the method of Hall et al so as to have employed the method in screening for antiviral agents that inhibit the replication of any of the viruses taught by Barney et al. As Hall et al's method requires detecting of viral mRNA, this modification would further require the design and use in Hall et al's method of primers and/or probes that provide a detectable signal "on the occurrence of the transcription" of a viral coding sequence. An ordinary artisan would have been motivated to have made such a modification in order to have identified agents useful in inhibiting the recited virus types, for the advantage of developing new and improved treatments for patients infected with said viruses. Accordingly, the combined teachings of Hall et al and Barney et al suggest the methods of claims 13-22.

22. Claims 23-25 and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Thomas et al (Clinical Science 97:207-213 [8/1999]) in view of Hall et al (U.S. Patent No. 6,218,105 B1 [04/17/2001; filed 01/07/2000; effective filing date 01/08/1999]).

Regarding the effective filing date of U.S. Patent No. 6,218,105, it is noted that the '105 patent claims the benefit of U.S. provisional application 60/115,220, filed January 8, 1999, and that the subject matter used to make the instant rejection is supported by the provisional application.

Thomas et al disclose a method in which the effects of ethidium bromide (EtBr) exposure on mitochondrial gene expression and nuclear gene expression are compared (see entire reference). Thomas et al teach that EtBr exposure is a known method of depleting mitochondrial DNA that is "employed to investigate the mechanisms underlying mitochondrial disorders," but that the effects of this treatment on nuclear DNA have not been established (see entire reference, particularly page 208). In Thomas et al's method, differential display reverse transcriptase PCR (DDRT-PCR) is used to establish the levels of expression of populations of mitochondrial genes and nuclear genes following growth of human thyroid cells in EtBr (see pages 208-209). It is a property of the method disclosed by Thomas et al that it assesses the toxicity of EtBr treatment on both mitochondrial and nuclear gene expression. The method employed by Thomas et al requires many steps to identify genes that are differentially expressed in the presence of EtBr, including mRNA isolation, DDRT-PCR, gel electrophoresis, elution and re-amplification of differentially displayed fragments, cloning, and

sequencing, as well as an additional step of Northern blot analysis to confirm differential expression (see pages 208-210). Thomas et al disclose that the expression of a limited number of nuclear genes in human thyroid cells is affected by EtBr treatment (see, e.g., pages 210-211), and that "the vast majority of mRNAs within a cell are quantitatively unaffected by EtBr treatment" (p. 212). Thomas et al do not disclose the use of an amplification reaction mixture that includes a "first primer and/or probe" that produces a detectable signal "on the occurrence on [sic] the transcription of host mitochondrial nucleic acids" and a "second primer and/or probe" that produces a second detectable signal "on the occurrence on [sic] the transcription of host nuclear nucleic acids," as required by the instant claims.

Hall et al disclose a method for "large scale screening of antiviral agents" (see entire reference, particularly, e.g., column 2, line 46-column 4, line 7). In embodiments of Hall et al's method, virions (both pre-incubated with a test agent and an untreated control) are used to infect host cells, and viral and host cell mRNA's are then PCR amplified in a single reaction mixture to determine the effects of the test agent on transcription (see col 2, line 46-column 4, line 7 [particularly col 2, lines 64-66, col 3, lines 38-39]; col 4, line 62-col 5, lines 1-8; col 5, lines 32-36; col 6, line 19-col 8, line 19 [particularly col 7, lines 56-67, describing real-time PCR detection of viral and cellular control transcripts in a single tube]). Hall et al disclose the use of both primers and probes that produce different detectable signals as indicators of viral nucleic acid transcription as compared to host nucleic acid transcription (see, e.g., col 7, line 56-col 8, line 1-19). It is also noted that Hall et al exemplify the use of their methods in

determining whether patient sera contains neutralizing antibodies capable of preventing HPV-11 replication (see, e.g., col 8, lines 51-64). While Hall et al primarily teach the use of their method in detecting and comparing viral and host transcription, Hall et al also state that their method "can further be applied to the high throughput screening of specific cellular mRNA transcripts" (see col 2, lines 59-60).

In view of the teachings of Hall et al, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Thomas et al so as to have employed the single tube method of Hall et al (rather than the labor intensive, multi-step method of Thomas et al) in assaying the effects of EtBr treatment on other types of cells. Specifically, it would have been obvious to one of skill in the art to have grown cells in the presence and absence of EtBr, and to have detecting in said cells, using the one-tube method of Hall et al, the levels of representative mitochondrial mRNAs and the nuclear mRNAs shown by Thomas et al to be affected by EtBr treatment. As Hall et al's method requires detection of target sequence mRNA molecules, this modification would further require the design and use in the method suggested by Thomas et al and Hall et al of primers and/or probes that provide a detectable signal "on the occurrence of the transcription" of both mitochondrial nucleic acids and nuclear nucleic acids. Thomas et al teach that there is a need for further studies "to confirm whether these genes [the genes differentially expressed in the human thyroid cells assayed by Thomas et al] are similarly affected" in other types of cell lines (see page 212). Hall et al teach that their method is rapid and does not require steps such as mRNA isolation or purification (see, e.g., col 9, lines 2-

3), and the single tube method exemplified by Hall et al requires fewer steps and provides for more rapid detection of expression levels than the method of Thomas et al. Accordingly, an ordinary artisan would have been motivated to have made such a modification in order to have determined the effects of EtBr treatment on other types of cells that might be used in the study of diseases associated with mitochondrial DNA defects, as suggested by Thomas et al, in a more rapid and efficient manner.

Regarding claims 24-25, it is noted that transcription of mitochondrial DNA results in the production of mitochondrial RNA, and that it is a property of the primers/probes suggested by Thomas et al in view of Hall et al that they would provide a detectable signal "on the occurrence of the transcription" of either mitochondrial DNA or mitochondrial RNA. Regarding claim 32, it is noted that Hall et al disclose detection of mRNA (as discussed above), and exemplify the use in their methods of mRNA as their indicator of transcription (see, e.g., Figure 2, col 3, lines 40-43; column 6, line 21-column 8, line 19 [particularly column 7, lines 56-67, describing real-time PCR detection of E2 and cellular control transcripts in a single tube]). It is a property of any mRNA (including the mRNA exemplified by Hall et al) that it is a "coding sequence", and further it is a property of the primers/probes suggested by Thomas et al and Hall et al that they would provide a detectable signal "on the occurrence" of the transcription of both host and mitochondrial nucleic acids that are coding sequences.

23. Claims 26-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Thomas et al in view of Hall et al, as applied to claims 23-25 and 32, above, in light of the teachings of Ojala et al (Nature 290:470-474 [4/1981]).

The teachings of Thomas et al and Hall et al are set forth in paragraph 22, above. It is again noted that the combined teachings of Thomas et al and Hall et al suggest detecting mitochondrial mRNA, and suggest the use of primers/probes that provide a detectable signal "on the occurrence of the transcription" of both mitochondrial nucleic acids and nuclear nucleic acids, as set forth above. The teachings of Ojala et al establish that the mitochondrial H strand is transcribed as a single polycistronic RNA molecule that is subsequently cleaved and processed into mRNAs (see entire reference, particularly page 473). Further, it is noted that it is a property of any mitochondrial transcription products that they are transcribed from mitochondrial DNA, which mitochondrial DNA comprises non-coding sequences including 5' and 3' non-coding sequences, as well as any mitochondrial gene introns. Accordingly, it is a property of the primers/probes suggested by Thomas et al in view of Hall et al that they would provide a detectable signal "on the occurrence of the transcription of host mitochondrial nucleic acids" that meet the requirements of claims 26-29, and therefore Thomas et al and Hall et al suggest the inventions of claims 26-29.

24. Claim 30 is rejected under 35 U.S.C. 103(a) as being unpatentable over Thomas et al (Clinical Science 97:207-213 [8/1999]) in view of Hall et al (U.S. Patent No. 6,218,105 B1 [04/17/2001; filed 01/07/2000; effective filing date 01/08/1999]), in light of the teachings of Ng et al (Molecular and Cellular Biology 5(10):2720-2732 [10/1985]).

Regarding the effective filing date of U.S. Patent No. 6,218,105, it is noted that the '105 patent claims the benefit of U.S. provisional application 60/115,220, filed

January 8, 1999, and that the subject matter used to make the instant rejection is supported by the provisional application.

This rejection applies to the claim to the extent that it is intended to be drawn to methods that require detection of a host nuclear nucleic acid that is a "non-coding sequence," and in which "the non-coding sequence is from β-actin." Please also see paragraph 7, above.

Thomas et al disclose a method in which the effects of ethidium bromide (EtBr) exposure on mitochondrial gene expression and nuclear gene expression are compared (see entire reference). Thomas et al teach that EtBr exposure is a known method of depleting mitochondrial DNA that is "employed to investigate the mechanisms underlying mitochondrial disorders," but that the effects of this treatment on nuclear DNA have not been established (see entire reference, particularly page 208). In Thomas et al's method, differential display reverse transcriptase PCR (DDRT-PCR) is used to establish the levels of expression of populations of mitochondrial genes and nuclear genes following growth of human thyroid cells in EtBr (see pages 208-209). It is a property of the method disclosed by Thomas et al that it assesses the toxicity of EtBr treatment on both mitochondrial and nuclear gene expression. The method employed by Thomas et al requires many steps to identify genes that are differentially expressed in the presence of EtBr, including mRNA isolation, DDRT-PCR, gel electrophoresis, elution and re-amplification of differentially displayed fragments, cloning, and sequencing, as well as an additional step of Northern blot analysis to confirm differential expression (see pages 208-210). Thomas et al disclose the detection of β-actin as a

nuclear RNA control (see page 210). Thomas et al disclose that the expression of a limited number of nuclear genes in human thyroid cells is affected by EtBr treatment (see, e.g., pages 210-211), and that "the vast majority of mRNAs within a cell are quantitatively unaffected by EtBr treatment" (p. 212). Thomas et al do not disclose the use of an amplification reaction mixture that includes a "first primer and/or probe" that produces a detectable signal "on the occurrence on [sic] the transcription of host mitochondrial nucleic acids" and a "second primer and/or probe" that produces a second detectable signal "on the occurrence on [sic] the transcription of host nuclear nucleic acids," as required by the instant claims.

Hall et al disclose a method for "large scale screening of antiviral agents" (see entire reference, particularly, e.g., column 2, line 46-column 4, line 7). In embodiments of Hall et al's method, virions (both pre-incubated with a test agent and an untreated control) are used to infect host cells, and viral and host cell mRNA's are then PCR amplified in a single reaction mixture to determine the effects of the test agent on transcription (see col 2, line 46-column 4, line 7 [particularly col 2, lines 64-66, col 3, lines 38-39]; col 4, line 62-col 5, lines 1-8; col 5, lines 32-36; col 6, line 19-col 8, line 19 [particularly col 7, lines 56-67, describing real-time PCR detection of viral and cellular control transcripts in a single tube]). Hall et al disclose the use of both primers and probes that produce different detectable signals as indicators of viral nucleic acid transcription as compared to host nucleic acid transcription (see, e.g., col 7, line 56-col8, line 1-19). Hall et al exemplify the detection of β-actin transcripts as an indicator of host cell gene transcription (see Figure 3 and col 8, lines 32-47). It is also noted that

Hall et al exemplify the use of their methods in determining whether patient sera contains neutralizing antibodies capable of preventing HPV-11 replication (see, e.g., col 8, lines 51-64). While Hall et al primarily teach the use of their method in detecting and comparing viral and host transcription, Hall et al also state that their method "can further be applied to the high throughput screening of specific cellular mRNA transcripts" (see col 2, lines 59-60).

In view of the teachings of Hall et al, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Thomas et al so as to have employed the single tube method of Hall et al (rather than the labor intensive, multi-step method of Thomas et al) in assaying the effects of EtBr treatment on other types of cells. Specifically, it would have been obvious to one of skill in the art to have grown cells in the presence and absence of EtBr, and to have detecting in said cells, using the one-tube method of Hall et al, the levels of representative mitochondrial mRNAs and the nuclear mRNAs shown by Thomas et al to be affected by EtBr treatment. As Hall et al's method requires detection of target sequence mRNA molecules, this modification would further require the design and use in the method suggested by Thomas et al and Hall et al of primers and/or probes that provide a detectable signal "on the occurrence of the transcription" of both mitochondrial nucleic acids and nuclear nucleic acids. Thomas et al teach that there is a need for further studies "to confirm whether these genes [the genes differentially expressed in the human thyroid cells assayed by Thomas et al] are similarly affected" in other types of cell lines (see page 212). Hall et al teach that their method is rapid and

does not require steps such as mRNA isolation or purification (see, e.g., col 9, lines 2-3), and the single tube method exemplified by Hall et al requires fewer steps and provides for more rapid detection of expression levels than the method of Thomas et al. Accordingly, an ordinary artisan would have been motivated to have made such a modification in order to have determined the effects of EtBr treatment on other types of cells that might be used in the study of diseases associated with mitochondrial DNA defects, as suggested by Thomas et al, in a more rapid and efficient manner.

Additionally, as both Thomas et al and Hall et al disclose the detection of β-actin RNA as a host nuclear gene control, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have included such a control in the method suggested by Thomas et al in view of Hall et al. As Hall et al's method requires detection of target sequence mRNA molecules, this modification would further require the design and use in the method suggested by Thomas et al and Hall et al of primers and/or probes that provide a detectable signal "on the occurrence of the transcription" of the β-actin gene. An ordinary artisan would have been motivated to have made such a modification in order to have confirmed that the reaction conditions employed allowed for the transcription of the constitutively expressed β-actin gene, for the advantage of ensuring the reliability and validity of results obtained with mitochondrial genes and the particular nuclear genes taught by Thomas et al. Ng et al disclose that it is a property of human β-actin mRNA that it includes non-coding sequences (see entire reference, particularly page 2725, including Figure 4). Thus, the teachings of Ng et al establish that it is a property of human β-actin mRNA that it is a

product of the transcription of "a non-coding sequence." Accordingly, it would be a property of the probes/primers employed in the method suggested by Thomas et al in view of Hall et al that they would provide a detectable signal "on the occurrence of the transcription" of a host nucleic acid that is a "non-coding sequence from β-actin." Accordingly, Thomas et al and Hall et al suggest the invention of claim 30.

25. Claim 31 is rejected under 35 U.S.C. 103(a) as being unpatentable over Thomas et al (Clinical Science 97:207-213 [8/1999]) in view of Hall et al (U.S. Patent No. 6,218,105 B1 [04/17/2001; filed 01/07/2000; effective filing date 01/08/1999]), in light of the teachings of Ercolani et al (The Journal of Biological Chemistry 263(30):15335-15341 [1988]).

Regarding the effective filing date of U.S. Patent No. 6,218,105, it is noted that the '105 patent claims the benefit of U.S. provisional application 60/115,220, filed January 8, 1999, and that the subject matter used to make the instant rejection is supported by the provisional application.

This rejection applies to the claim to the extent that it is intended to be drawn to methods that require detection of a host nuclear nucleic acid that is a "non-coding sequence," and in which "the non-coding sequence is from GAPDH." Please also see paragraph 7, above.

Thomas et al disclose a method in which the effects of ethidium bromide (EtBr) exposure on mitochondrial gene expression and nuclear gene expression are compared (see entire reference). Thomas et al teach that EtBr exposure is a known method of depleting mitochondrial DNA that is "employed to investigate the mechanisms

underlying mitochondrial disorders," but that the effects of this treatment on nuclear DNA have not been established (see entire reference, particularly page 208). In Thomas et al's method, differential display reverse transcriptase PCR (DDRT-PCR) is used to establish the levels of expression of populations of mitochondrial genes and nuclear genes following growth of human thyroid cells in EtBr (see pages 208-209). It is a property of the method disclosed by Thomas et al that it assesses the toxicity of EtBr treatment on both mitochondrial and nuclear gene expression. The method employed by Thomas et al requires many steps to identify genes that are differentially expressed in the presence of EtBr, including mRNA isolation, DDRT-PCR, gel electrophoresis, elution and re-amplification of differentially displayed fragments, cloning, and sequencing, as well as an additional step of Northern blot analysis to confirm differential expression (see pages 208-210). Thomas et al disclose the detection of GAPDH as a nuclear RNA control (see Figure 1 and page 210). Thomas et al disclose that the expression of a limited number of nuclear genes in human thyroid cells is affected by EtBr treatment (see, e.g., pages 210-211), and that "the vast majority of mRNAs within a cell are quantitatively unaffected by EtBr treatment" (p. 212). Thomas et al do not disclose the use of an amplification reaction mixture that includes a "first primer and/or probe" that produces a detectable signal "on the occurrence on [sic] the transcription of host mitochondrial nucleic acids" and a "second primer and/or probe" that produces a second detectable signal "on the occurrence on [sic] the transcription of host nuclear nucleic acids," as required by the instant claims.

Hall et al disclose a method for "large scale screening of antiviral agents" (see entire reference, particularly, e.g., column 2, line 46-column 4, line 7). In embodiments of Hall et al's method, virions (both pre-incubated with a test agent and an untreated control) are used to infect host cells, and viral and host cell mRNA's are then PCR amplified in a single reaction mixture to determine the effects of the test agent on transcription (see col 2, line 46-column 4, line 7 [particularly col 2, lines 64-66, col 3, lines 38-39]; col 4, line 62-col 5, lines 1-8; col 5, lines 32-36; col 6, line 19-col 8, line 19 [particularly col 7, lines 56-67, describing real-time PCR detection of viral and cellular control transcripts in a single tube]). Hall et al disclose the use of both primers and probes that produce different detectable signals as indicators of viral nucleic acid transcription as compared to host nucleic acid transcription (see, e.g., col 7, line 56-col8, line 1-19). Hall et al disclose the use in their methods of GAPDH transcripts as a host cell mRNA control (see, e.g., col 7, lines 1-67; column 8, lines 1-19). It is also noted that Hall et al exemplify the use of their methods in determining whether patient sera contains neutralizing antibodies capable of preventing HPV-11 replication (see, e.g., col 8, lines 51-64). While Hall et al primarily teach the use of their method in detecting and comparing viral and host transcription, Hall et al also state that their method "can further be applied to the high throughput screening of specific cellular mRNA transcripts" (see col 2, lines 59-60).

In view of the teachings of Hall et al, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Thomas et al so as to have employed the single tube method of Hall et al

(rather than the labor intensive, multi-step method of Thomas et al) in assaying the effects of EtBr treatment on other types of cells. Specifically, it would have been obvious to one of skill in the art to have grown cells in the presence and absence of EtBr, and to have detecting in said cells, using the one-tube method of Hall et al, the levels of representative mitochondrial mRNAs and the nuclear mRNAs shown by Thomas et al to be affected by EtBr treatment. As Hall et al's method requires detection of target sequence mRNA molecules, this modification would further require the design and use in the method suggested by Thomas et al and Hall et al of primers and/or probes that provide a detectable signal "on the occurrence of the transcription" of both mitochondrial nucleic acids and nuclear nucleic acids. Thomas et al teach that there is a need for further studies "to confirm whether these genes [the genes differentially expressed in the human thyroid cells assayed by Thomas et al] are similarly affected" in other types of cell lines (see page 212). Hall et al teach that their method is rapid and does not require steps such as mRNA isolation or purification (see, e.g., col 9, lines 2-3), and the single tube method exemplified by Hall et al requires fewer steps and provides for more rapid detection of expression levels than the method of Thomas et al. Accordingly, an ordinary artisan would have been motivated to have made such a modification in order to have determined the effects of EtBr treatment on other types of cells that might be used in the study of diseases associated with mitochondrial DNA defects, as suggested by Thomas et al, in a more rapid and efficient manner.

Additionally, as both Thomas et al and Hall et al disclose the detection of GAPDH RNA as a host nuclear gene control, it would have been *prima facie* obvious to one of

ordinary skill in the art at the time the invention was made to have included such a control in the method suggested by Thomas et al in view of Hall et al. As Hall et al's method requires detection of target sequence mRNA molecules, this modification would further require the design and use in the method suggested by Thomas et al and Hall et al of primers and/or probes that provide a detectable signal "on the occurrence of the transcription" of the GAPDH gene. An ordinary artisan would have been motivated to have made such a modification in order to have confirmed that the reaction conditions employed allowed for the transcription of the constitutively expressed GAPDH gene, for the advantage of ensuring the reliability and validity of results obtained with mitochondrial genes and the particular nuclear genes taught by Thomas et al. Ercolani et al disclose that it a property of human GAPDH mRNA that it includes non-coding sequences (see entire reference, particular page 15335, right column, and Figure 3). Thus, the teachings of Ercolani et al establish that it is a property of the primers/probes to GAPDH suggested by Thomas et al in view of Hall et al that they would provide a detectable signal "on the occurrence of the transcription" of a host nucleic acid that is a "non-coding sequence from GAPDH." Accordingly, Thomas et al and Hall et al suggest the invention of claim 31.

Conclusion

26. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Diana B. Johannsen whose telephone number is 703/305-0761. The examiner can normally be reached on Monday-Friday, 7:30 am-4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones can be reached at 703/308-1152. The fax phone numbers for the organization where this application or proceeding is assigned are 703/872-9306 for regular communications and 703/872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703/308-0196.

Diana B. Johannsen
April 23, 2003